

What is claimed is:

1. A method of preventing or treating a disease, such as a disease characterized by cell proliferation and infiltration of inflammatory cells, coronary diseases, hypertension, renal diseases, diabetes, or ocular diseases and conditions in a mammal, which comprises administering pharmaceutically effective amounts of a combination of:

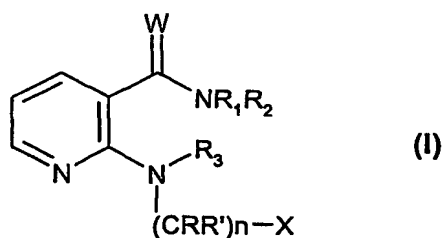
(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of:

- i. angiostatic steroids;
- ii. photosensitizers;
- iii. implants containing corticosteroids;
- iv. AT1 receptor antagonists;
- v. ACE inhibitors;
- vi. cyclooxygenase inhibitors;
- vii. IGF-IR inhibitors;
- viii. mTOR kinase inhibitors;
- ix. somatostatin receptor antagonists;
- x. PI3K inhibitors;
- xi. Raf kinase inhibitors;
- xii. PKC inhibitors;
- xiii. integrin antagonists;
- xiv. endogenous anti-angiogenic molecules; and
- xv. PEDF and analogs.

2. The method according to claim 1, wherein the VEGF inhibitor compound is

(i) of the formula (I)



wherein

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

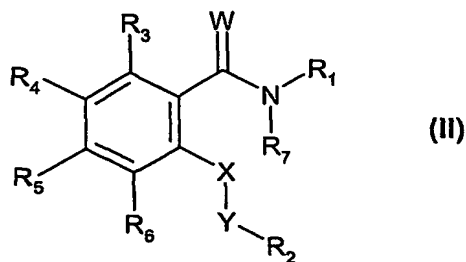
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or poly-substituted;

or of an *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt;

(ii) of the formula (II)



wherein

W is O or S;

X is NR_8 ;

Y is $CR_9R_{10}-(CH_2)_n$,

wherein

R_9 and R_{10} are, independently, of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO_2 ;

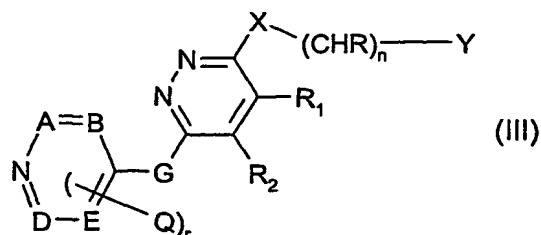
R_1 is aryl;

R_2 is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R_2 cannot represent 2-phthalimidyl, and in case of $Y = SO_2$ cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3 , R_4 , R_5 and R_6 , independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8 , independently of each other, are H or lower alkyl;
or of an *N*-oxide; or a pharmaceutically acceptable salt thereof; or

(iii) of the formula (III)



wherein

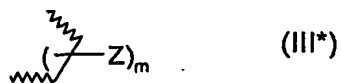
r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

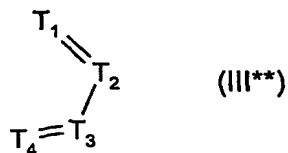
R_1 and R_2 (i) are lower alkyl or

(ii) together form a bridge in subformula (III*)



the binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula (III**)



wherein one or two of the ring members T_1 , T_2 , T_3 and T_4 are nitrogen, and the others are in each case CH, and the binding is achieved via T_1 and T_4 ;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-S-}$, $-\text{CH}_2\text{-NH-}$, oxa ($-\text{O-}$), thia ($-\text{S-}$), or imino ($-\text{NH-}$);

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or unsubstituted or substituted cycloalkyl;
and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom, or a pharmaceutically acceptable salt of such compound having at least one salt-forming group.

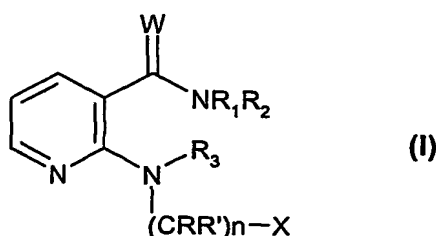
3. The method according to claim 1, wherein the VEGF inhibitor compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof.

4. The method according to claim 1, which comprises administering pharmaceutically effective amounts of a combination of:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of BPD-MA, lumiracoxib, celecoxib, rofecoxib, everolimus, SOM230, octreotide, QAN697, anecortave, triamcinolone, fluocinolone, dexamethasone, valsartan and benazepril.

5. The method according to claim 4, wherein the VEGF inhibitor compound is
(i) of the formula (I)



wherein

n is from 1 up to and including 6;

W is O or S;

R₁ and R₃ represent independently of each other hydrogen, lower alkyl or lower acyl;

R₂ represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

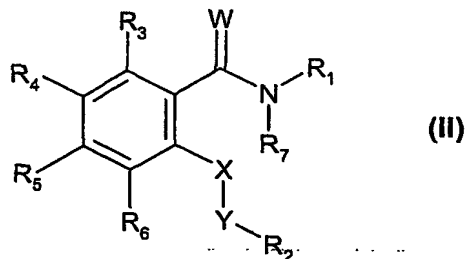
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or poly-substituted;

or of an N-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt;

(ii) of the formula (II)



wherein

W is O or S;

X is NR₈;

Y is CR₉R₁₀-(CH₂)_n,

wherein

R₉ and R₁₀ are, independently, of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO₂;

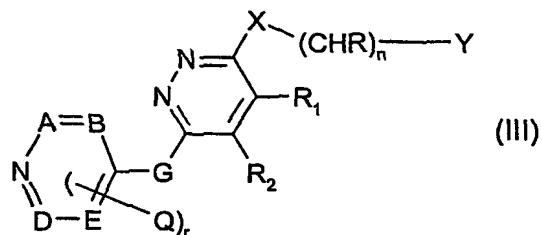
R₁ is aryl;

R₂ is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R_3 , R_4 , R_5 and R_6 , independently of the other, is H or a substituent other than hydrogen; and

R_7 and R_8 , independently of each other, are H or lower alkyl;
or of an *N*-oxide; or a pharmaceutically acceptable salt thereof; or

(iii) of the formula (III)



wherein

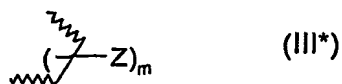
r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

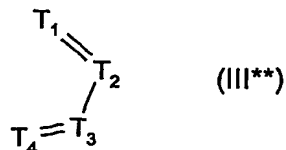
R_1 and R_2 (i) are lower alkyl or

(ii) together form a bridge in subformula (III*)



the binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula (III**)



wherein one or two of the ring members T_1 , T_2 , T_3 and T_4 are nitrogen, and the others are in each case CH, and the binding is achieved via T_1 and T_4 ;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-S-}$, $-\text{CH}_2\text{-NH-}$, oxa ($-\text{O-}$), thia ($-\text{S-}$), or imino ($-\text{NH-}$);

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or unsubstituted or substituted cycloalkyl;
and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom, or a pharmaceutically acceptable salt of such compound having at least one salt-forming group.

6. The method according to claim 4, wherein the VEGF inhibitor compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising:

(a) a VEGF inhibitor compound; and

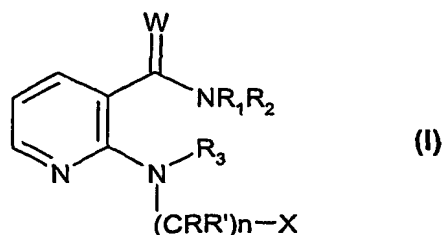
(b) one or more second therapeutic agents selected from the group consisting of:

- i. angiostatic steroids;
- ii. photosensitizers;
- iii. implants containing corticosteroids;
- iv. AT1 receptor antagonists;
- v. ACE inhibitors;
- vi. cyclooxygenase inhibitors;
- vii. IGF-IR inhibitors;
- viii. mTOR kinase inhibitors;
- ix. somatostatin receptor antagonists;
- x. PI3K inhibitors;
- xi. Raf kinase inhibitors;

- xii. PKC inhibitors;
- xiii. integrin antagonists;
- xiv. endogenous anti-angiogenic molecules; and
- xv. PEDF and analogs.

8. The pharmaceutical composition according to claim 7, wherein the VEGF inhibitor compound is

(i) of the formula (I)



wherein

n is from 1 up to and including 6;

W is O or S;

R₁ and R₃ represent independently of each other hydrogen, lower alkyl or lower acyl;

R₂ represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

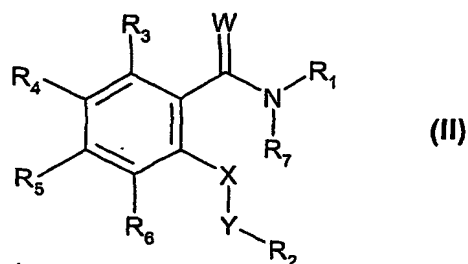
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or poly-substituted;

or of an *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt;

(ii) of the formula (II)



wherein

W is O or S;

X is NR₈;

Y is CR₉R₁₀-(CH₂)_n,

wherein

R₉ and R₁₀ are, independently, of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO₂;

R₁ is aryl;

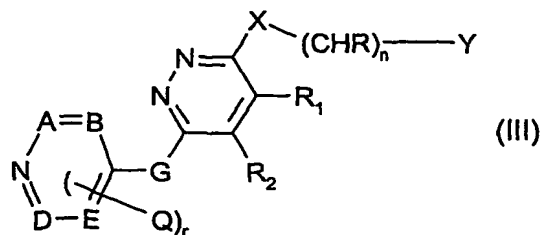
R₂ is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R₃, R₄, R₅ and R₆, independently of the other, is H or a substituent other than hydrogen; and

R₇ and R₈, independently of each other, are H or lower alkyl;

or of an N-oxide; or a pharmaceutically acceptable salt thereof; or

(iii) of the formula (III)



wherein

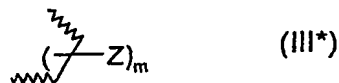
r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

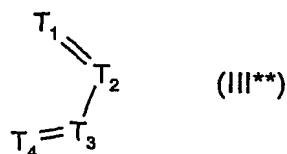
R₁ and R₂ (i) are lower alkyl or

(ii) together form a bridge in subformula (III*)



the binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula (III**)



wherein one or two of the ring members T₁, T₂, T₃ and T₄ are nitrogen, and the others are in each case CH, and the binding is achieved via T₁ and T₄;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, -CH₂-O-, -CH₂-S-, -CH₂-NH-, oxa (-O-), thia (-S-), or imino (-NH-);

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or unsubstituted or substituted cycloalkyl; and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom, or a pharmaceutically acceptable salt of such compound having at least one salt-forming group.

9. The pharmaceutical composition according to claim 7, wherein the VEGF inhibitor compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof.

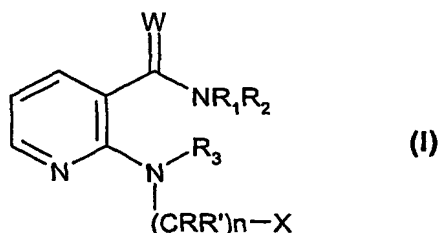
10. The pharmaceutical composition according to claim 7 comprising:

(a) a VEGF inhibitor compound; and

(b) one or more second therapeutic agents selected from the group consisting of BPD-MA, lumiracoxib, celecoxib, rofecoxib, everolimus, SOM230, octreotide, QAN697, anecortave, triamcinolone, fluocinolone, dexamethasone, valsartan and benazepril.

11. The pharmaceutical composition according to claim 10, wherein the VEGF inhibitor compound is

(i) of the formula (I)



wherein

n is from 1 up to and including 6;

W is O or S;

R_1 and R_3 represent independently of each other hydrogen, lower alkyl or lower acyl;

R_2 represents an cycloalkyl group, an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or polysubstituted;

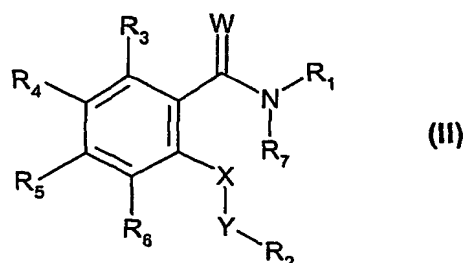
R and R' are independently of each other hydrogen or lower alkyl; and

X represents an aryl group, or a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms and 0, 1 or 2 heteroatoms independently from each other selected from the group consisting of oxygen and sulfur, which groups in each case are unsubstituted or mono- or poly-substituted;

or of an *N*-oxide or a possible tautomer thereof;

or of a pharmaceutically acceptable salt;

(ii) of the formula (II)



wherein

W is O or S;

X is NR₈;

Y is CR₉R₁₀-(CH₂)_n,

wherein

R₉ and R₁₀ are, independently, of each other hydrogen or lower alkyl; and

n is an integer of from and including 0 to and including 3; or

Y is SO₂;

R₁ is aryl;

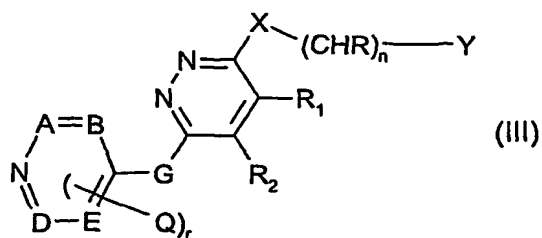
R₂ is a mono- or bicyclic heteroaryl group comprising one or more ring nitrogen atoms with the exception that R₂ cannot represent 2-phthalimidyl, and in case of Y = SO₂ cannot represent 2,1,3-benzothiadiazol-4-yl;

any of R₃, R₄, R₅ and R₆, independently of the other, is H or a substituent other than hydrogen; and

R₇ and R₈, independently of each other, are H or lower alkyl;

or of an N-oxide; or a pharmaceutically acceptable salt thereof; or

(iii) of the formula (III)



wherein

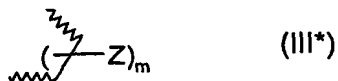
r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

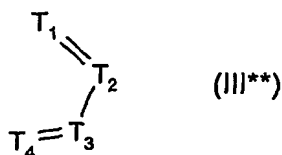
R₁ and R₂ (i) are lower alkyl or

(ii) together form a bridge in subformula (III*)



the binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula (III**)



wherein one or two of the ring members T₁, T₂, T₃ and T₄ are nitrogen, and the others are in each case CH, and the binding is achieved via T₁ and T₄;

A, B, D, and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, -CH₂-O-, -CH₂-S-, -CH₂-NH-, oxa (-O-), thia (-S-), or imino (-NH-);

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or unsubstituted or substituted cycloalkyl; and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom, or a pharmaceutically acceptable salt of such compound having at least one salt-forming group.

12. The pharmaceutical composition according to claim 10, wherein the VEGF inhibitor compound is 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof.

13. The method of claim 1, wherein the disease is selected from psoriasis; restenosis, e.g., stent-induced restenosis; endometriosis; Crohn's disease; arthritis, such as rheumatoid arthritis; hemangioma; angiofibroma; ocular diseases, such as exudative form of age-related macular degeneration (Wet AMD), age-related macular degeneration (Dry AMD), macular edema, diabetic macular edema (DME), cystoid macular edema (CME), diabetic retinopathy, proliferative diabetic retinopathy (PDR), ischemic retinopathy, ocular neovascularization such as choroidal neovascularization, retinal neovascularization, iris neovascularization and corneal neovascularization, retinopathy of prematurity, neovascular glaucoma, central vein occlusion, after effects of corneal transplantation, ocular histoplasmosis and pathologic myopia; renal diseases, such as glomerulonephritis; diabetic nephropathy; malignant nephrosclerosis; thrombotic microangiopathic syndromes; transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver; mesangial cell-proliferative diseases; arteriosclerosis; injuries of the nerve tissue and for inhibiting the re-occlusion of vessels after balloon catheter treatment; for use in vascular prosthetics or after inserting mechanical devices for holding vessels open, such as, e.g., stents; as immunosuppressants; as an aid in scar-free wound healing; and for treating age spots and contact dermatitis.

14. The method according to claim 1, wherein the disease is selected from inflammation, rheumatoid arthritis, asthma, chronic bronchitis, arteriosclerosis and transplant rejection.